EPIGENETIC MODIFICATION OF NEURAL GENES BY THE NEURON RESTRICTIVE SILENCER FACTOR

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The Neuron Restrictive Silencer Factor (NRSF) is the master transcriptional repressor of the neural phenotype and has been shown to regulate hundreds of neural genes. It is becoming very clear that NRSF maintains repression of gene expression by recruiting chromatin modifiers to target gene regions. Previous work of ours showed that the small molecules, forskolin and isobutylmethylxanthine (IBMX), could induce neural-like differentiation in mesenchymal stem cells by causing downregulation of NRSF and de-repression of neural gene expression[1]. We next set out to determine if there were epigenetic changes in the promoter regions of NRSF target genes. In our work, we look at changes in the methylation of DNA in the promoter regions through bisulfite conversion and sequencing, as well as the acetylation status of nearby histones through ChIP. NRSF is also dysregulated in several neurological diseases. In particular, repression of certain ion channels involved in the electrophysiological properties of neurons may underlie conditions such as neuropathic pain and epilepsy. Work has shown that in the disease state the genes for these ion channels show repressive epigenetic marks[2]. Using dCas9, we are able to bring chromatin modifiers to specific regions of the genome. Here, we use a dCas9-Tet1 fusion to demethylate NRSF regulated genes. As a proof of principle, we show that by reversing repressive epigenetic marks on genes that contribute to neurological disease, that the epigenetic activity of NRSF itself could be a therapeutic dimension.

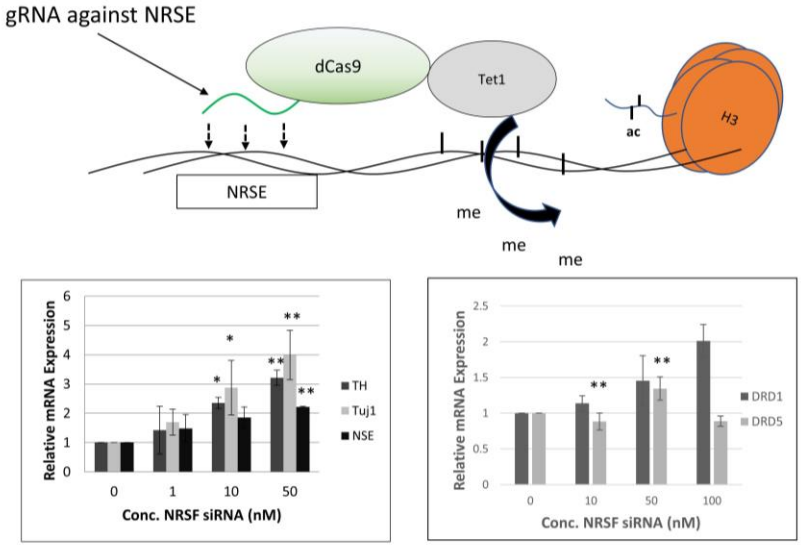

Figure 1 – Downregulation of NRSF causes de-repression of several neural genes. dCas9 fused to chromatin modifiers could reverse repressive epigenetic marks and guided to NRSF controlled genes.

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